REMARKS

The Official Action dated April 11, 2005 has been carefully considered. Accordingly, the amendments and remarks presented herein are believed sufficient to overcome the rejections of the Examiner and place the present application in condition for allowance.

The specification is amended to correct an accession number that was erroneously transcribed. Applicants appreciate the Examiner bringing this to their attention.

Substitute pages of the Sequence Listing are submitted in order to bring the disclosed sequence listings in compliance with Rule 1.822(c)(5), which requires all sequences to be set forth in the 5' to 3' direction. In addition, two computer readable copies of the corrected sequence listing, and a Sequence Identity Statement are submitted in accordance with the sequence rules.

Claim 1 is amended for matters of form and to clarify that the function is determined by correlating the polymorphism to an alpha-2B-adrenergic receptor function. Claims 2-4 are amended for matters of form and clarity. Claims 6-15 are cancelled. Claim 16 is amended for matters of form and to incorporate the subject matter of dependent claim 18. Accordingly, claim 18 is cancelled. Claim 20 is amended to correct a typographical error. Claim 30 is cancelled. Claim 31 is amended for clarity and to incorporate the subject matter of claim 32. Accordingly claim 32 is cancelled. Claims 33 and 34 are amended for matters of form and clarity. Claim 38 is amended for matters of form and to incorporate the subject matter of claim 39. Accordingly, claim 39 is cancelled. Claims 40-42 are amended for clarity according to suggestions by the Examiner. Claim 63 is amended to clarify that the function is determined by correlating the polymorphism to a predetermined alpha-2B-

adrenergic receptor function. New claims 65-67 have been added in accordance with the teachings in the specification at page 8, paragraphs 3 and 4.

As these amendments are not believed to constitute new matter, Applicants submit that entry is in order and is therefore respectfully requested. Claims 1-64 are currently pending and claims 1-22, 30-44 and 63 are under examination.

Objection to Specification

The Examiner objected to several informalities in the Specification. First, the Examiner notes that there is an inconsistency between the actual identity of GenBank record AF009500 and the assertion that it contains the sequence of the gene encoding α2B-adrenergic receptor. Applicants appreciate the Examiner bringing this to their attention and have secured the correct number and amended the specification accordingly (see Amendments to the Specification, supra). Applicants note that the origin of this error appears to be in typographical, as the "95" portion is present in the correct Accession number, with 0's replacing the remaining numerals. Hence, this rejection basis has been overcome and reconsideration is respectfully requested.

Second, the Examiner asserts that the teaching of SEQ ID NO: 5 as the complement of SEQ ID NO: 3 is inaccurate, and, similarly, the teaching of SEQ ID NO: 6 as the complement of SEQ ID NO: 4 is inaccurate. Applicants agree that the sequence and its complement were set forth, inadvertently, in opposing directions and have corrected the sequences to comport with Rule 1.82(c)(5). A paper copy of substitute sheets of the sequence listing reflecting the amended sequences, along with two discs comprising the full CRF sequence listing reflecting the amended sequence listings are submitted herewith. Also, the

requisite Sequence Identity Statement is attached hereto. Accordingly, the objections have been overcome and reconsideration is respectfully requested.

Claim Objections

Claims 20 and 30 were objected to for containing typographical errors. Applicants appreciate the Examiner pointing these out and have corrected them accordingly.

Claim Rejections

35 U.S.C. § 112, first paragraph

Claims 13-15 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, and, specifically, for being amended to contain new matter. However, Applicants note that this rejection has been mooted by the cancellation of claims 6-15.

Claims 31-44 are rejected under 35 U.S.C. § 112 first paragraph as failing to comply with the enablement requirement. Specifically the Examiner asserts that the claims are all drawn to methods of identifying an individual at increased risk for developing a disease associated with an alpha-2B-adrenergic receptor molecule or methods for diagnosing or prognosing an individual with a disease associated with an alpha-2B-adrenergic receptor molecule, and the methods recite the detection of a particular polymorphism within the gene encoding the receptor such that, according to the Examiner, "practice of the claimed invention requires a knowledge of at least a predictive association between the polymorphism and a disease." The Examiner maintains that "the specification does not contain a single working example or guidance concerning which diseases are associated with which alleles of this polymorphism," and that "determination of an association between a polymorphism and a

disease is an empirical endeavor," and concludes that it would take undue experimentation to practice the invention. This rejection is traversed and reconsideration is respectfully requested.

Instant claim 31 is directed to a method for identifying an individual at increased risk for developing a disease associated with an alpha-2B-adrenergic receptor molecule comprising: a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or a fragment or a complement of the polynucleotide from the individual; and b. detecting in the sample a polymorphism at a polymorphic site located at nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or a complement thereof, wherein the polymorphism correlates to the disease, thereby identifying the individual at increased risk for the disease, wherein the disease is selected from the group consisting of cardiovascular disease, central nervous system disease, and combinations thereof.

As Applicants set forth in the present Specification (e.g. page 3, bottom of the page, bridging to the top of page 4; page 8, second full paragraph;), the alpha-2BAR modulates a variety of physiological functions, and that a relationship exists between receptor signaling functions and certain physiological responses/functions. The present invention provides methods utilizing a particular polymorphism, useful to clinicians because the polymorphism itself manifests phenotypically as a receptor exhibiting measurable altered receptor signaling function. Applicants teach that the altered receptor signaling directly relates to certain diseases so that the polymorphism correlates, one step removed, to those certain diseases.

On page 10, paragraph 1, Applicants specifically discuss Alpha-2B adrenergic receptor diseases. "Disease" is defined therein to include "any condition manifested as one or

more physical and/or psychological symptoms for which treatment is desirable, and includes previously and newly identified diseases and other disorders." Specific diseases currently recognized as correlated to such altered functioning are listed on page 10, lines 11-18. As recited in present independent claim 31, Applicants have discovered a correlation, in particular, to cardiovascular disease, central nervous system disease, and combinations thereof.

The phrase "correlate the polymorphic site with a disease" is defined in the present specification as including "associating the polymorphism which occurs at a higher allelic frequency or rate in individuals with the disease than individuals without the disease" (page 11, lines 25-27). And further, the specification provides guidance on how to accomplish "correlation" of a disease with a polymorphism by reference to known bio-statistical methods (page 11, lines 27-28, bridging to page 12, lines 1-2).

The Examiner asserts that determining an association between a polymorphism and a disease is an empirical endeavor, and that the specification does not provide examples or guidance such that this endeavor would require undue experimentation. Applicants submit that this view of what information is required to enable the present invention is misconstrued. In addition, while Applicants admit that some experimentation may be required, the nature of that experimentation is routine as it involves carrying out well-known laboratory procedure directed to obtaining samples, detecting the presence or absence of the polymorphism in the sample, and correlating this result to a known risk for cardiovascular disease, central nervous system disease, or combinations thereof.

As noted, Applicants teach that the relevant correlation is determined statistically, not empirically. Hence, the empirically-based aspect, that is, the knowledge that a particular

disease is associated with a particular alteration in receptor function, is assumed to pre-exist. The invention provides a correlative link between this association and the presence of a polymorphism such that identification of the polymorphism in an individual provides information about a disease propensity or state of the individual.

The enablement mandate of § 112, first paragraph, as interpreted into case law, requires that the specification must provide sufficient teaching such that one skilled in the art can make and use the full scope of the invention without undue experimentation. *CFMT, Inc. v. Yieldup Int'l Corp.*, 68 USPQ2d 1940, 1944; *In re Wands*, 8 USPQ2d 1400, 1405 (Fed. Cir. 1988). "The key word is 'undue,' not experimentation.'" *Wands*, 8 USPQ2d at 1405 (citation omitted). The specification must enable one of ordinary skill in the art to practice "the full scope of the claimed invention." *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Clarifying this principle, the Federal Circuit has explained: "That is not to say that the specification itself must necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art." *Id.*

Applicants respectfully submit that the inventive method as defined by instant claim 31 merely requires two empirical steps, each of which are fully enabled by the disclosure. Hence, the art at issue in the inventive methods is primarily statistical, which is highly predicatable. That is, the method requires a practitioner to, essentially, obtain a sample from an individual and detect a polymorphism in the sample, wherein the polymorphism correlates to a particular disease. The third step, to identify an individual at risk for the disease, presupposes, as required by the wherein clause, that the polymorphism correlates (statistically) to a disease. Hence, with respect to the empirical activity necessary to practice

the invention, Applicants submit that it does not involve undue experimentation, and further submit that the present specification provides sufficient detail and guidance to enable a person of ordinary skill in the art to practice the invention. Therefore, the rejection of claim 31, and claims 32-44 dependent therefrom, under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement has been overcome. Reconsideration is respectfully requested.

35 U.S.C. § 112, second paragraph

Claims 2-5, 8-11, 13-15, 18, 33-36 and 40-43 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter.

First, Applicants note that claims 8-11 and 13-15 have been cancelled. Therefore, the rejection with respect to those claims is moot and will not be addressed.

Claim 2 is asserted to be indefinite because it is "not clear what it means for a polymorphism to comprise a particular sequence." Instant claim 2 recites, as per the Examiner's suggestion: "A method according to claim 1, wherein the polynucleotide comprises SEQ ID NO: 3 or 4, or a complement thereof, at the polymorphic site." Hence the rejection is overcome and reconsideration is respectfully requested.

Claim 3 is asserted to be indefinite over the recitation of the language "wherein the polymorphism is an insertion of 9 nucleotides at nucleotide positions 901 to 909 of SEQ ID NO: 1," because the claim does not set forth what the insertion is relative to. Applicants appreciate the Examiner's suggestion and instant claim 3 now recites "a method according to claim 2, wherein the polymorphism is an insertion of nine nucleotides into SEQ ID NO: 2

immediately after position 900 of SEQ ID NO: 2." Hence, the rejection has been overcome and reconsideration is respectfully requested.

Claim 4 is asserted to be indefinite for reasons analogous to claim 3, set forth above. In accordance with the Examiner's suggestion, instant claim 4 is directed to a method according to claim 2, wherein the polymorphism is a deletion of nucleotides 901 to 909 from SEQ ID NO: 1. Hence, the rejection has been overcome and reconsideration is respectfully requested.

Claim 5 is asserted to be indefinite due to failure to follow the required convention for directionally setting forth sequence listings. As the sequence listing has been amended to adhere to these rules and thereby clarify the identity of the recited complements, the rejection has been overcome and reconsideration is respectfully requested.

Claim 18 is rejected as indefinite over the inclusion of SEQ ID NO:s 17-18 in the claim. Specifically, the Examiner notes that claim 16 requires an oligonucleotide "having a nucleotide sequence that is complementary to a region of the polynucleotide, and which, when hybridized to the region permits the identification of the nucleotide present at the polymorphic site of the polynucleotide," but that SEQ ID NO:s 17-18 are identified in the specification as being primers that specifically hybridize to M13 vectors, not to a "polymorphic site" within the polynucleotide of the instant claims. Thus the Examiner asserts that it is unclear how or whether SEQ ID NO:s 17-18 might function in the methods of the claims as written.

Applicants note that these two sequences set forth as SEQ ID NO: 17 and 18 correspond to the M13 forward and reverse universal sequencing primers and that they are contained within the 5' end of each sense and antisense primer as taught on page 57, Example

1, of the present specification. There were inadvertently included in this claim as part of a more comprehensive list of oligonucleotides suitable for use in the present inventive methods found, for example, on page 21 of the present specification. SEQ ID NO: 17 and SEQ ID NO: 18 have been accordingly deleted from the recitation of sequences in claim 18 so that the rejection has been overcome and reconsideration is respectfully requested.

Claim 33 is asserted as being indefinite because "it is not clear what is meant for a 'polymorphism' to comprise a particular sequence." Claim 33 has been amended for clarification and now recites " [T]he method according to claim 31, wherein the polynucleotide comprises SEQ ID NO: 3 or SEQ ID NO: 4, or a complement thereof, at the polymorphic site." Hence, the rejection has been overcome and reconsideration is respectfully requested.

Claim 34 is asserted to be indefinite over the recitation of the language "wherein the polymorphism is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." Specifically, the Examiner asserts that the claim is not clear because it does not set forth what the insertion is relative to and that, as written, the claim appears to require that the polymorphism to be detected includes an insertion into instant SEQ ID NO: 1, which is the intact wild type allele, contrary to the teachings of the specification.

Instant claim 34 now recites " [T]he method according to claim 31, wherein the polymorphism is an insertion of nine nucleotides into SEQ ID NO: 2 immediately after position 900 of SEQ ID NO: 2. The claim is now clear as to the position of insertion and therefore the rejection has been overcome. Reconsideration is respectfully requested.

Claim 35 is asserted to be indefinite for reasons analogous to the above stated reasons with respect to claim 34. Specifically the Examiner asserts that it is not clear if the claim is

requiring an additional deletion of nine nucleotides from SEQ ID NO: 2 as it is recited or if the claim intends to recite that the sequence with the deletion is SEQ ID NO: 2.

Instant claim 35 now recites "[T]he method according to claim 31, wherein the polymorphism is a deletion of nucleotides 901 to 909 from SEQ ID NO: 1." Applicants submit that the position of deletion and the resultant sequence are clarified. Hence, the rejection has been overcome and reconsideration is respectfully requested.

Claim 36 is asserted to be indefinite because "SEQ ID NO: 5 and SEQ ID NO: 6 are not the complement of SEQ ID NO: 3 or SEQ ID NO: 4" in accordance with the convention set forth in Rule 1.822(c)(5), which requires that the nucleotides set forth in a sequence listing are provided in the 5' to 3' direction, from left to ride. Applicants appreciate the Examiner bringing this oversight to their attention and have corrected the sequence listing accordingly. Hence, this rejection has been overcome and reconsideration is respectfully requested.

Claim 40 is asserted to be indefinite because "it is not clear what it means for a 'polymorphism' to comprise a particular sequence." Specifically, the Examiner notes that the polymorphism itself cannot comprise a sequence since it is not a molecule but a variation between two molecules.

Instant claim 40 now recites "[t]he method according to claim 38, wherein the polynucleotide comprises SEQ ID NO: 3 or SEQ ID NO: 4, or a complement thereof, at the polymorphic site." Applicants submit that it clear the polynucleotide, and not the polymorphism, that comprises one of the alternative sequences. Hence the rejection has been overcome and reconsideration is respectfully requested.

Claim 41 is asserted to be indefinite over the recitation of the language "wherein the polymorphism is an insertion of 9 nucleotides at nucleotide position 901 to 909 of SEQ ID NO: 1." Specifically, the Examiner asserts that the claim "is not clear because it does not set forth what the insertion is relative to," and that SEQ ID NO: 1 is the sequence for the wild type molecule which has all of the nucleotides intact."

Instant claim 41 now recites "[t]he method according to claim 38, wherein the polymorphism is an insertion of nine nucleotides into SEQ ID NO: 2 immediately after position 900 of SEQ ID NO: 2. Applicants submit that this claim language is clear as to the position of insertion and as to the sequence of the polymorphism being described. Hence, the rejection has been overcome and reconsideration is respectfully requested.

Claim 42 is asserted to be indefinite for reasons analogous to the reasons specified with respect to claim 41, above. In this case the Examiner maintains that it is not clear from the claim language that, as taught in the specification, instant SEQ ID NO: 2 has a deletion relative to SEQ ID NO 1.

Instant claim 42 recites "[t]he method according to claim 38, wherein the polymorphism is a deletion of nucleotides 901 to 909 from SEQ ID NO: 1. Applicants submit that this recitation is now clear as to the polymorphism being described and in how the deletion compares to the wild type allele as set forth in SEQ ID NO: 1. Hence, the rejection has been overcome and reconsideration is respectfully requested.

Claim 43 is asserted to be indefinite because "SEQ ID NO: 5 and SEQ ID NO: 6", as set forth, are not the complements of SEQ ID NO: 3 or SEQ ID NO: 4 as required by the claims. Applicants appreciate the Examiner pointing out the convention required by sequence rule 1.822(c)(5) and have amended the sequence listing accordingly.

For the reasons detailed specifically with respect to each claim above, Applicants submit that the rejection of claims 2-5, 8-11, 13-15, 18, 33-36 and 40-43 under 35 U.S.C. § 112, second paragraph, have been overcome and reconsideration is respectfully requested.

35 U.S.C § 102

Claims 1-14, 16-17, 20-22, 31-44, and 63 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Heinonen et al. The Journal of Clinical Endocrinology & Metabolism, July 1999) ("Heinonen"). First, Applicants note that claims 6-15, 32 and 39 have been cancelled and the rejection with respect to those claims is therefore moot. As to the remaining claims, specifically, the Examiner asserts that Heinonen teaches a deletion of nine nucleotides, in frame, of the alpha-2B-adrenergic receptor molecule that results in the loss of three glutamic acid residues from the encoded polypeptide, and that the sequence deleted is identical to instant SEQ ID NO: 3. The Examiner also asserts that the present specification teaches that the deletion taught in this reference is identical to the deletion identified in this application. The Examiner maintains that Heinonen teaches that this deletion polymorphism is "associated with reduced BMR in obese, non-diabetic patients" and suggests a mechanism related to the "possible incapability of the encoded deletion polypeptide of being phosphorylated and desensitized in the normal manner." The Examiner maintains that the polymorphism detected by Heinonen is a addition or deletion of nine nucleotides at positions 901-909 of SEQ ID NO: 1 or 2 (see, e.g. Office Action page 18, top of the page).

With respect specifically to instant **claim 1** the Examiner asserts that Heinonen teaches the manipulative steps (a) and (b) and that claim 1 does not contain steps which relate to the preamble or give it patentable weight.

With respect specifically to instant **claim 31**, the Examiner asserts that Heinonen teaches a method of identifying an individual at increased risk for developing a disease

associated with an alpha-2BAR molecule comprising instantly recited steps (a) and (b), and states that Heinonen teaches that alleles of the polymorphism are associated with reduced BMR in obese subjects, and by extension are a predictor of an increased risk of developing obesity.

With regard specifically to instant **claim 38**, the Examiner repeats the analysis of claim 31, set forth above, and further states that the preamble recitation of a method for diagnosing or prognosing an individual with a disease associated with alpha-2BAR molecules are considered inherently met by Heinonen.

With regard specifically to instant claims **32 and 39**, the Examiner asserts that Heinonen teaches "determining a predisposition to obesity," and that this, "by extension suggests an increased likelihood of a wide variety of cardiovascular diseases that are related to obesity."

With respect specifically to instant claim **63**, the Examiner again asserts that Heinonen teaches the recited manipulative steps and the preamble language is not considered relevant to patentability since there are no method steps which relate to it. The Examiner further details the rejection bases of the dependent claims.

These rejections are traversed and reconsideration is respectfully requested.

Instant **claim 1** is directed to a method of determining alpha-2B-adrenergic receptor function by detecting a polymorphism at a polymorphic site in a polynucleotide encoding an alpha-2B-adrenergic receptor molecule. The method comprises: a. obtaining a sample of a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or a fragment or a complement of the polynucleotide; b. detecting in the sample a polymorphism at a polymorphic site, wherein the polymorphic site is located at nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or a complement thereof; and c. correlating the

polymorphism to a predetermined alpha-2B-adrenergic receptor function, thereby determining the function.

Instant independent claim 63 is directed to a method of determining alpha-2B-adrenergic receptor function by indirectly detecting a polymorphism at a polymorphic site in a polynucleotide encoding an alpha-2B-adrenergic receptor molecule. The method comprises: a. obtaining a sample comprising a polynucleotide encoding an alpha-2B-adrenergic receptor molecule, wherein the polynucleotide, or a fragment or a complement thereof, comprises SEQ ID NO: 1 or 2 ; and b. indirectly detecting in the sample the polymorphism at the polymorphic site located at nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or a complement thereof; and c. correlating the polymorphism to a predetermined alpha-2B-adrenergic receptor function, thereby determining the function.

Applicants further note that claims 1 and 63 have been amended to add a correlative step such that the polymorphism is correlated to an alpha-2BAR function, thereby determining the function. This step expressly relates the recitation of the preamble to the method, and, therefore, under prevailing claim interpretation rules, Applicants submit that the preamble recitation carries patentable weight.

Notably, Heinonen fails to disclose or suggest cellular mechanisms and fails to provide any disclosure related to alpha-2BAR functioning. Heinonen does not employ, disclose, or fairly suggest methods of using the presently disclosed polymorphism to determine alpha-2BAR receptor function. Heinonen merely suggests that a possible mechanism underlying the fairly weak association discovered between BMR, heart rate and a polymorphism may be that variant receptors are "incapable of being phosphorylated and desensitized in the normal manner." and basis this suggestion on a reference authored in part by one of the Applicants, that is related to alpha-2CAR functioning ("[a]n acidic motif within the third intracellular loop of the α_2C2 adrenergic receptor is required for agonist-promoted

phosphorylation and desensitization," *Biochemistry.* 34:11946–11953). It is significant to note that this reference suggests mechanisms related specifically to the "C" subtype of the adrenergic receptor. Indeed, rather than suggesting that one may determine alpha-2BAR receptor functioning by detecting the polymorphism, Heinonen posits several alternative theories, including blood flow redistribution due to regional vascular resistance as mechanistic underpinnings to the observed decreased heart rate in the homozygous variant population.

Heinonen merely suggests mechanisms for phenotypic outcomes based on cellular mechanisms posited for other known phenotypic outcomes, and, more specifically, suggests mechanistic underpinnings based on the known phenotypic manifestations, for example, vascular restriction, to their observed phenotypic manifestations. Heinonen does not teach or suggest methods directed to determining a2BAR receptor functioning by detecting a polymorphism, and does not experimentally investigate nor offer data between any suggested cellular or molecular mechanisms and a2BAR polymorphisms.

Heinonen neither investigates nor discloses anything related to alpha-2BAR *functioning*. Moreover, Heinonen fails to disclose a method comprising, *inter alia*, the step of correlating the polymorphism to a predetermined alpha-2B-adrenergic receptor function, thereby determining the function. Hence, Heinonen does not anticipate independent claim 1, or claims 2-5 dependent therefrom, or instant claim 63.

Instant **claim 16** is directed to a method of genotyping an individual by genotyping a polynucleotide encoding an alpha-2B-adrenergic receptor molecule from a sample of the individual. The method comprises: a. isolating from the individual a sample having a polynucleotide encoding an alpha-2B adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or a fragment or a complement of the polynucleotide; b. subjecting the polynucleotide to an incubation with at least one oligonucleotide, the at least one oligonucleotide having a

nucleotide sequence that is complementary to a region of the polynucleotide, and which, when hybridized to the region permits the identification of nucleotides present at a polymorphic site of the polynucleotide, wherein the incubation is under conditions sufficient to allow specific hybridization to occur between complementary nucleic acid molecules; c. permitting hybridization to occur; and d. identifying the polymorphic site to obtain the genotype of the individual, wherein the polymorphic site comprises a polymorphism comprising an insertion or deletion of 9 nucleotides at nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2. The claim further specifies that the at least one oligonucleotide is selected from the group consisting of: a list of 7 explicitly recited oligonucleotides, specifically set forth as SEQ ID NOS: 14, 15, 16, 19, 20, 21, 22, and complementary sequences thereof.

Heinonen fails to teach the oligonucleotides required to be employed by the method set forth in instant independent claim 16.

Instant **claim 31** is directed to a method for identifying an individual at increased risk for developing a disease associated with an alpha-2B-adrenergic receptor molecule. The method comprises: a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or a fragment or a complement of the polynucleotide from the individual; and b. detecting in the sample a polymorphism at a polymorphic site located at nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or a complement thereof, wherein the polymorphism correlates to the disease, thereby identifying the individual at increased risk for the disease. The disease is selected from the group consisting of cardiovascular disease, central nervous system disease, and combinations thereof.

Instant **claim 38** is directed to a method for diagnosing or prognosing an individual with a disease associated with an alpha-2B-adrenergic receptor molecule. The method

comprises: a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or 2 or a fragment or a complement of the polynucleotide from the individual; b. detecting in the sample a polymorphism at a polymorphic site located at nucleotide positions 901 to 909 of SEQ ID NO: 1 or 2 or a complement thereof, and c. correlating the polymorphism to the disease. The disease comprises a cardiovascular disease, a central nervous system disease, or combinations thereof.

Heinonen, on the other hand, teaches the significance of mediation of the alpha-2-adrenergic receptors on regulation of energy balance. Heinonen screened the entire coding sequence of the a2BAR gene and identified a polymorphism leading to deletion of three glutamic acids (Glu x 12) at amino acid positions 297-309 (see Figure 1, "The missing codons are either 297–299 or 298–300) in the third intracellular loop of the a2BAR. Specifically Heinonen investigated the association of the polymorphism to basal metabolic rate, taught to be a known risk factor for obesity, by conducting an association analysis of obesity-related phenotypic variables with the identified deletion polymorphism in a sample of 58 *obese*, nondiabetic Finns.

The very specific phenotypic data points collected by Heinonen are BMR and heart rate. The difference noted in homozygous individuals in BMR was less than 100 Calories per day. "The magnitude in the difference in adjusted BMR between the subject groups with two long alleles and two short alleles was approximately 5.6%, or 94 Cal/day." Heinonen specifically notes that "a large proportion of the obese subjects in our study population had two normal receptor alleles, and no significant differences were observed between the genotypic groups in the severity of obesity (page 7, para 5).

Applicants submit that it is an unreasonable stretch for the Examiner to equate a phenotypic variance in BMR of 100 Calories per day, or a non-pathological decrease in heart

rate, as in any way equivalent to obesity, or even one step further removed, to cardiovascular disease as presently recited. . Further, the Examiner's assertion that the phenotypic difference in BMR is a "predictor" of obesity is nonsensical in light of the fact that all of the Heinonen subjects were obese to begin with, regardless of whether they possessed the polymorphism. The Heinonen study simply was not designed and did not establish that the polymorphism is, or is not a predictor of obesity, or that the phenotypic difference of 100 Calories per day is or is not, a predictor of obesity, since all the Heinone subjects were obese. Indeed, as noted above, Heinonen admits that even within this obese population, "no significant differences were observed between the genotypic groups in the severity of obesity."

In addition, Heinonen fails to disclose methods for identifying individuals at increased risk for developing a disease associated with an a2BAR receptor molecule as required by instant independent claim **31**. In fact, Heinonen investigates correlations between BMR and heart rate and an a2BAR polymorphism, neither of which are considered by one of ordinary skill in the art to be "diseases," "disorders," or anything synonymous, particularly at the level disclosed by Heinonen. To the extent Heinonen could be said to make any association between these phenotypic characteristics and obesity, any such association is clouded by the pre-selection of the study population *for* obesity, and Heinonen admits that a large proportion of the obese subjects were homozygous normal for the a2BAR receptor. Applicants submit that it is the Examiner who is asserting that the Heinonen study impliedly yields some predicative value, but this is not supported due to the deficiencies of the Heinonen study protocals.

Similarly, Heinonen fails to teach or suggest a method for diagnosing or prognosing an individual with a disease as required by instant claim **38**. Heinonen attempts to correlate a polymorphism with BMR and heart rate. Heinonen makes no conclusory statements as to the correlation between these phenotypic characteristics and obesity, or, further, to

cardiovascular disease. Significantly, Heinonen does not define obesity as a disease but as the result of a combination of factors, including BMR and heart rate. Indeed, the supposed correlate between the variant receptor and obesity itself is so tenuous that Heinonen cautions against considering presence of the variant receptor as predictive of anything. The obese subjects of Heinonen possessed an average BMI of 34%, regardless of whether they possessed the polymorphism.

Anticipation under 35 U.S.C. § 102(b) requires the disclosure in a single prior art reference of each element of the claims under consideration, *Alco Standard Corp. v. TVA*, 1 U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986). Moreover, "It is well settled that prior art under 35 U.S.C. § 102(b) must sufficiently describe the claimed invention to have placed the public in possession of it." *Elan Pharmaceuticals Inc. v. Mayo Foundation for Medical Education and Research*, 68 USPQ2d 1373 (Fed. Cir. 2003). Heinonen does not teach determination of a2BAR function based on detecting a polymorphism comprising, inter alia, correlating the polymorphism to an alpha-2BAR receptor function as required by instant independent claim 1, and does not teach such a determination based on indirectly detecting a polymorphism, as required by independent claim 63. Heinonen fails to teach a method of genotyping an individual by genotyping a polynucleotide encoding an alpha-2BAR molecule from a sample of the individual that comprise, inter alia, employment of one or more of the oligonucleotides set forth in the Markush group recited in instant independent claim 16. Heinonen does not teach methods of identifying individuals at risk for developing a disease associated with an alpha-2BAR molecule, wherein the disease is cardiovascular disease, central nervous system disease, or a combination thereof. Heinonen merely states a weak association to BMR and heart rate, both disclosed phenotypes being within normal ranges and not representative of disease states. Further, Heinonen fails to teach or disclose methods for diagnosing or

prognosing an individual with cardiovascular disease, a central nervous system disease, or combinations thereof, as required by independent claim 38.

Hence, the rejection of claims 1-5, 16-17, 20-22, 33-38, 40-44, and 63 under 35 U.S.C. §102(b) over Heinonen has been overcome. Reconsideration is respectfully requested.

Claims 1-6, 8-13, 16, 20-21 and 63 are rejected under 35 U.S.C. § 102(b) as being anticipated by Jewell-Motz et al. Biochemistry, Vol. 34 1995, pages 11946-11953 ("JM"), as cited in the IDS. Again, Applicants point out that claims 6-15 have been cancelled so that the rejection with respect to these claims is moot, and this response is therefore addressed as to the rejection of claims 1-5, 16, 20-21 and 63. Specifically the Examiner asserts that Jewell-Motz used a site-directed mutagenesis to delete or substitute a 16 amino acid stretch of glutamic acid residues from the alpha-2B-adrenergic receptor molecule and that the deleted sequence "would inherently include instant SEQ ID NO: 3 which encodes three glutamic acid residues within a 16 amino acid repeat sequence of glutamic acids in the alpha-2B-adrenergic receptor molecule. Further, the Examiner asserts that Jewell-Motz teaches that the deletion of and substitution of this amino acid section results in receptors that undergo agonist-promoted phosphorylation at levels of only about 44 and 50% respectively, relative to the wild type, and that after the site-directed mutagenesis of the nucleic acid encoding the wild-type alpha-2B-adrenergic receptor molecule, presence of the mutations were detected using nucleotide tracking and sequencing; and that final constructs were analyzed using restriction analysis and sequencing to confirm the presence of the desired mutation.

Independent claims 1, 16, and 63 are set forth in detail above.

First, Applicants note that JM is work preliminary to the instant invention and was co-authored by one of the present inventors. JM discloses manipulations, including additions and deletions, of a 16-amino acid stretch of glutamic acid residues from the alpha-2B-

adrenergic receptor molecule, and suggests that this 16-amino acid sequence constitutes a polymorphism in the alpha-2BAR sequence. The present inventors, on the other hand, discovered that the polymorphism is actually 3-amino acid sequence, albeit within this larger sequence.

Applicants respectfully submit that the Examiner made an error in asserting JM as an §102, rather than §103 reference. In contravention to established case law, the Examiner equated the broadly disclosed polymorphism in JM with the narrower polymorphism employed in the present inventive methods. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (holding that where the "prior art ... discloses a range encompassing a somewhat narrower claimed range," the narrower range may be obvious). The polymorphism disclosed by JM is larger and includes elements superfluous to the portion of the sequence the present invention sets forth as permitting the desirable correlative properties. Applicants assert that, while the 16-amino acid polypeptide disclosed by JM broadly encompasses the polymorphism employed in the present inventive methods, identifying the precise amino acid sequence which actually constitutes the polymorphism is advantageous over the broader disclosure because detecting the polymorphism is easier and more accurate than detecting the 16 amino acid sequence of JM. Indeed, the opportunity for error will be much reduced in methods dependent upon the detection of a 3-amino acid sequence polymorphism versus a 16-amino acid sequence polymorphism. Hence, Applicants assert that the JM-disclosed polymorphism would negatively alter and may even preclude the functioning and efficacy of the presently inventive methods, if employed therein, in place of the presently disclosed 3-amino acid polymorphism.

Further and significantly with respect to independent claims 1 and 63, JM fails to teach or disclose any methods of determining alpha-2BAR function by detecting the polymorphism in a polynucleotide encoding the alpha 2-BAR receptor molecule. JM, as the

Examiner notes, only makes an observation that the receptors comprising the polymorphism differ in agonist-promoted phosphorylation from the wild type. However, JM fails to disclose methods related to this, and in particular, methods of determining alpha-2BAR functioning by, inter alia, correlating the polymorphism to an alpha-2BAR function, thereby determining the function, as set forth in instant claims 1 and 63.

Further, instant independent claim 16, which is directed to a method that employs one or more of several expressly set forth oligonucleotides, can not be anticipated by JM , in part, because JM does not enable the method so defined. First, JM fails to teach or disclose the oligonucleotides set forth in claim 16. Second, if the polymorphism of JM were substituted into the method of 16 in place of the presently recited polymorphism, the oligonucleotides disclosed may fail to detect it since they are based on primer design derived from the 3-amino acid sequence polymorphism.

Anticipation under 35 U.S.C. § 102(b) requires the disclosure in a single prior art reference of each element of the claims under consideration, *Alco Standard Corp.* 1 U.S.P.Q.2d at 1341. The corollary of the rule is that absence from the reference of any claimed element negates anticipation. *Kloster Speedsteel AB v. Crucible Inc.*, 793 F.2d 1565, 230 USPQ 81 (Fed.Cir. 1986). JM fails to disclose methods of determining alpha-2BAR function by detecting a polymorphism at a polymorphic site in a polynucleotide encoding an alpha-2BAR molecule, comprising, *inter alia*, detecting a polymorphism located at nucleotide positions 901-909 of SEQ ID NOS 1 or 2, or a complement thereof; and correlating the polymorphism to an alpha 2-BAR function, thereby determining the function, and as required in instant independent claim 1. Further, JM fails to disclose methods of determining alpha-2BAR function by indirectly detecting a polymorphism at a polymorphic site in a polynucleotide encoding an alpha-2BAR molecule, comprising, *inter alia*, indirectly detecting a polymorphism located at nucleotide positions 901-909 of SEQ ID NOS 1 or 2, or

a complement thereof; and correlating the polymorphism to an alpha 2-BAR function, thereby determining the function, and as required in instant independent claim 63. And, JM fails to disclose methods of genotyping an individual by genotyping a polynucleotide encoding an alpha-2BAR molecule from a sample of the individual, comprising, *inter alia*, subjecting the polynucleotide to an incubation with at least one oligonucleotide selected from a specified list as recited in claim 16, and identifying a polymorphic site to obtain the genotype, wherein the polymorphic site comprises a polymorphism comprising an insertion of deletion of 9 nucleotides at nucleotide positions 901 to 909 of SEQ ID NOS: 1 or 2, as required in instant independent claim 16.

Further, to serve as an anticipating reference, the reference must enable that which it is asserted to anticipate. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). Since JM discloses a larger polypeptide (and, therefore, the polynucleotide encoding it), the specific oligonucleotides set forth in instant claim 63 would not likely be similarly efficacious. Further, the practice of all of the inventive methods would be less precise and more error prone, as is understood by those of ordinary skill in the art to be typically the case when one is attempting to detect larger, less specific polynucleotides.

Hence, the rejection of independent claims 1, 16 and 63, and claims 2-5, and 20-21 dependent therefrom, under 35 U.S.C. §102 has been overcome. Reconsideration is therefore respectfully requested.

35 U.S.C. § 103

Claim 18 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Heinonen in view of Baldwin et al. (American Journal of Hypertension 12:853-857 [9/1999] ("Baldwin") and Newton ("Chapter 6: Primers" in PCZR Essential Data, C.R. Newton, ed.,

John Wiley & Sons, Chichester, 1995, pages 49-56). Specifically, the Examiner sets forth the teachings of Heinonen as noted above, but notes that Heinonen fails to teach the oligonucleotides recited in instant claim 18, including, in particular, the oligonucleotide presently identified by SEQ ID NO:.13. The Examiner asserts Baldwin for explicitly teaching this oligonucleotide, and Newton for general teachings as to the design of PCR primer pairs.

First, Applicants note that the previous claim 18 has been cancelled and most of the subject matter was incorporated into independent claim 16. Claim 16 is set forth in detail above. However, the particular subject matter asserted by the Examiner as disclosed by Baldwin was not incorporated. The oligonucleotide presently identified as SEQ ID NO: 13, and disclosed by Balwin, is no longer the subject matter of a present claim. This oligonucleotide was included in a Markush grouping of oligonucleotides discovered by the instant inventors as suitable for carrying out the method defined by instant claim 16. As the combination of Heinonen over Baldwin in view of Newton does not teach or disclose the method of claim 16, the rejection of claim 16 (having the subject matter of prior claim 18) under 35 U.S.C. §103 has been overcome. Reconsideration is respectfully requested.

Claim 19 is rejected under 35 U.S.C. § 103(a) over Heinonen in view of U.S. Patent Application Serial No. 2001//0016338 A1 to Snapir et al. Specifically the Examiner asserts that, with regard to independent claim 16, Heinonen teaches a method of genotyping a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising: (a) obtaining a sample comprising the polynucleotide; and (b) performing a primer extension reaction employing an oligonucleotide comprising at least one nucleotide comprising a nucleotide sequence homologous to a nucleotide sequence located at position 901 to 909 of SEQ ID NO: 1 or SEQ ID NO: 2. The Examiner further asserts that Heinonen performs a PCR reaction that utilizes a primer that comprises sequence GAA which is identical to a

nucleotide sequence located between positions 901 to 909 of SEQ ID NO: 1, and that the PCR methods taught by Heinonen meet all the limitations of claim 16, but that Heinonen does not teach a method for detection of the polymorphism using one of the specific hybridization methodologies recited in claim 19.

Instant claim 16, however, has been amended to incorporate the limitations of dependent claim 18, as set forth in detail above. As noted above, Heinonen does not teach or suggest methods of genotyping an individual by genotyping a polynucleotide encoding an alpha-2B-adrenergic receptor molecule from a sample of the individual comprising, inter alia, subjecting the polynucleotide to an incubation with at least one oligonucleotide selected from the group consisting of the list of sequences as set forth in claim 16 by the recited SEQ ID NO's. The teachings of Snapir do not cure this deficiency of the primary reference.

To establish prima facie obviousness of the claimed invention, all the claim limitations must be taught or suggested by the prior art, *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). The combination of Heinonen in view of Snapir fails to teach all of the recited limitations of instant independent claim 16. It is axiomatic that a claim depending from a nonobvious claim is nonobvious as well. Hence, the rejection of claim 19, which depends from nonobvious claim 16, under 35 U.S.C. §103 over Heinonen in view of Snapir has been overcome. Reconsideration is respectfully requested.

Claim 30 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Ho et al. (American Journal of Meidcal Genetics, Vol 81, No. 6, p. 510, Abstract #93) ("Ho") in view of Heinonen. However, Applicants note that the subject matter of claim 30 has been cancelled and that this rejection is therefore moot.

It is believed that the above represents a complete response to the Office Action dated March 11, 2004, and to the rejections of claims 1-22, 30-44 and 63 under 35 U.S.C. §§ 112,

first paragraph, 112, second paragraph, 102(b) and 103(a). Reconsideration and an early allowance are respectfully requested.

Respectfully submitted,

By: _____

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